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INTERACTION OF DERIVATIVES OF 7-AMINO-1,5-BENZO-DIAZEPIN-2-ONES WITH α,β-UNSATURATED KETONES

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Derivatives of new condensed heterosystems, the tetracyclic [1,4]diazepino[3,2,1-hi]pyrido-[4,3,2-cd]indoles and tricyclic [1,4]diazepino[2,3-g]- and -[2,3-f]quinolines have been synthesized by the interaction of 7-amino-4-phenyl(or methyl)-1,3,4,5-tetrahydro(or 1,3-dihydro)-2H-1,5-benzodiazepin-2-ones with dimethyl 2-oxoglutaconate and methyl 4-oxo-2-pentenoate. The corresponding carboxylic acids of the new derivatives were synthesized by alkaline hydrolysis of the methyl esters. The direction of the cyclocondensation reaction was determined by both the structure of the diazepine ring of the initial amines and also by the structure of the α,β-unsaturated ketones. Quantum-chemical calculations have been carried out of the minimal values of the local energy of ionization and of the resonance stabilization energy on specific atoms of the initial amines.

Keywords: 7-amino-1,5-diazepin-2-one, dimethyl 2-oxoglutaconate, methyl 4-oxopentenoate, local energy of ionization, cyclocondensation, resonance stabilization energy.

Previously we investigated the interaction of 7-(or 8-, or 9-)amino-4-methyl-1-(or 5-)alkyl-substituted tetrahydro-1,5-benzodiazepin-2-ones with dimethyl 2-oxoglutaconate with the aim of obtaining condensed heterosystems containing a dicarboxy-substituted diazepinoquinoline fragment [1, 2]. It was established that the direction of the cycloaddition reaction depends both on the position of the primary amino group in the benzene ring of the benzodiazepinone, and on the presence of a substituent in positions 1 and 5 of the diazepine ring. It was also shown that quantum-chemical calculations of the minimal values of the local ionization energy (I_{min}) on the electron density surface of the molecules and the resonance stabilization energy of the initial amines fortunately demonstrate the tendency of activation and deactivation of the benzene ring [2, 3]. The possibility of using quantum-chemical calculations to determine the direction of ring formation of quinolines was followed in [4]. Continuing the investigations of the synthesis of condensed systems of 1,5-benzodiazepinone, we considered in the present work the direction of closure of the pyridine ring on interacting derivatives of 7-amino-4-phenyl(or methyl)-1,3,4,5-tetra-hydro(or 1,3-dihydro)-2H-1,5-benzodiazepin-2-ones with α,β-unsaturated ketones under the conditions of the modified Debner–Müller reaction.

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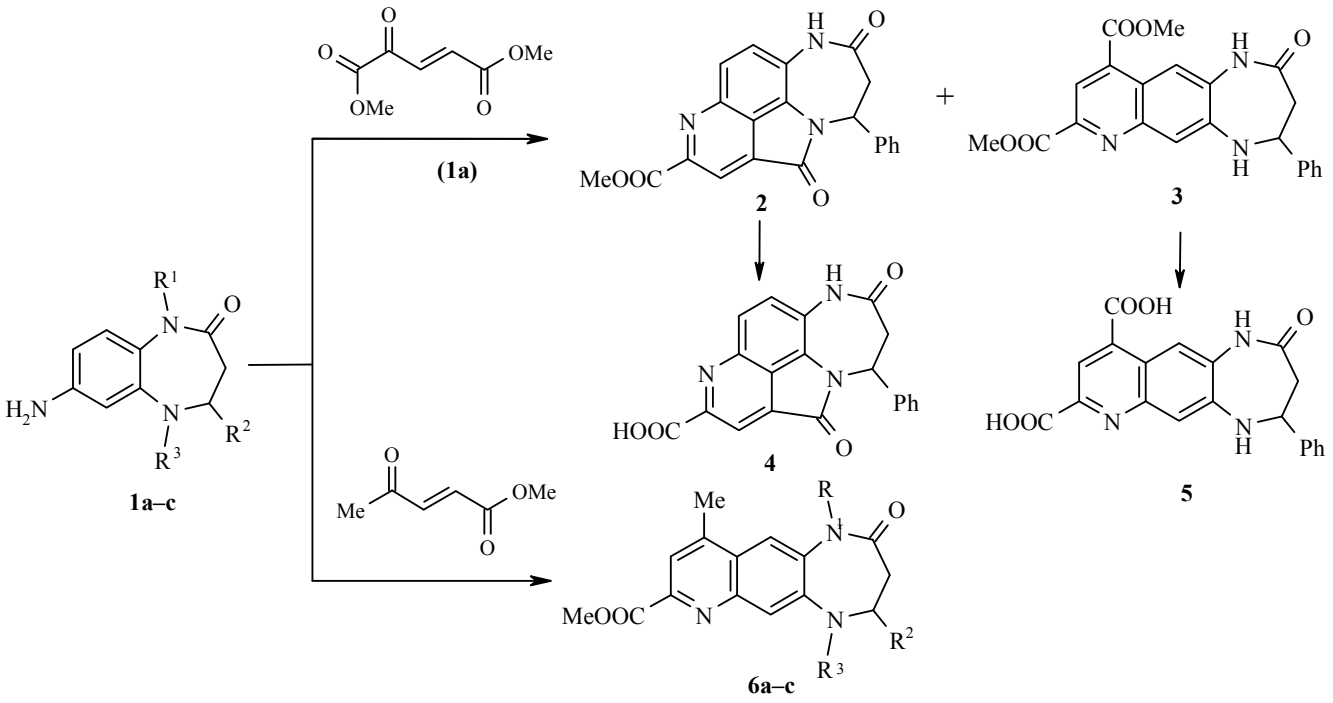
Scheme 1



1, **6 a** $R^1 = R^3 = H$, $R^2 = Ph$; **b** $R^1 = H$, $R^2 = R^3 = Me$; **c** $R^1 = R^2 = Me$, $R^3 = H$

The cyclocondensation reaction of the appropriate amino components **1a-c** (Scheme 1) and **7** (Scheme 2) with an excess of dimethyl 2-oxoglutaconate or methyl 4-oxo-2-pentenoate was carried out in dichloromethane solution at room temperature for 24 h with subsequent addition of 3 N HCl solution in glacial acetic acid to dehydrate and aromatize the intermediate piperidinol derivative [5]. Thus on interacting 7-amino-4-phenylbenzodiazepinone **1a** with dimethyl 2-oxoglutaconate two products were obtained, tetracyclic [1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]indole **2** and tricyclic [1,4]diazepino[2,3-*g*]quinoline **3** (Scheme 1, Table 1).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	Yield, %
		C	H	N		
2	$C_{21}H_{15}N_3O_4$	67.47 / 67.56	4.17 / 4.05	11.10 / 11.25	339-341 ($CHCl_3$)	21
3	$C_{22}H_{19}N_3O_5$	65.25 / 65.18	4.87 / 4.72	10.19 / 10.37	149-151 (EtOAc–Et_2O)	25
4	$C_{20}H_{13}N_3O_4$	66.53 / 66.85	3.47 / 3.65	11.83 / 11.69	283 (decomp.) (H_2O)	61
5	$C_{20}H_{15}N_3O_5$	63.37 / 63.66	4.19 / 4.01	11.01 / 11.14	301-303 (H_2O)	79
6a	$C_{21}H_{19}N_3O_3$	69.87 / 69.79	5.23 / 5.30	11.51 / 11.63	268-270 (MeOH)	47
6b	$C_{17}H_{19}N_3O_3$	65.30 / 65.16	6.17 / 6.11	13.33 / 13.41	228-230 (EtOAc)	35
6c	$C_{17}H_{19}N_3O_3$	65.02 / 65.16	6.08 / 6.11	13.49 / 13.41	223-225 (Et_2O)	33
8	$C_{22}H_{17}N_3O_5$	65.64 / 65.50	4.21 / 4.25	10.29 / 10.42	310-312 (*i*-PrOH–*t*-BuMeO)	19
10	$C_{21}H_{21}N_3O_4$	66.59 / 66.48	5.51 / 5.58	11.26 / 11.08	96-100* (*i*-PrOH–H_2O)	52

*Amorphous substance, no sharply expressed melting point.

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **1a**, **2-5**, **6a-c**, **7-10**

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
2	3239, 3175, 1727, 1675, 1651, 1632	3.36 (1H, dd, *J* = 2.8, *J* = 14.8, CH_2); 3.50 (1H, dd, *J* = 5.5, *J* = 14.9, CH_2); 4.01 (3H, s, OCH_3); 5.94 (1H, dd, *J* =2.7, *J* = 5.6, CH); 7.22-7.38 (5H, m, H Ar); 7.59 (1H, d, *J* = 9.2, H-10); 7.97 (1H, d, *J* = 9.2, H-11); 8.52 (1H, s, H-3); 10.68 (1H, br. s, NH)
3	3319, 3196, 724, 1676	2.85 (1H, br. dd, CH_2); 2.98 (1H, dd, *J* = 10.3, *J* = 13.7, CH_2); 4.05 (3H, s, OCH_3); 4.09 (3H, s, OCH_3); 4.57 (1H, br. s, NH); 5.11 (1H, dd, *J* = 3.6, *J* = 10.3, CH); 7.30-7.42 (5H, m, H Ar); 7.74 (1H, s, H-6); 8.53 (1H, s, H-11); 8.55 (1H, s, H-9); 8.56 (1H, br. s, NH)
4	3263-2557, 1723, 1672, 1647, 1627	3.25-3.55 (2H, br. m, CH_2); 5.94 (1H, br. dd, CH); 7.23-7.37 (5H, m, H Ar); 7.58 (1H, d, *J* = 9.1, H-10); 7.95 (1H, d, *J* = 9.1, H-11); 8.50 (1H, s, H-3); 10.68 (1H, br. s, NH)
5	3269-2544, 1690-1620	2.82 (2H, br. m, CH_2); 5.07 (1H, br. m, CH); 6.93 (1H, br. s, NH); 7.31 (1H, br. m, H-4'); 7.39 (2H, br. m, H-3',5'); 7.48 (2H, br. m, H-2',6'); 7.70 (1H, s, H-6); 8.24 (1H, s, H-11); 8.41 (1H, s, H-9); 10.29 (1H, br. s, NH)
6a	3359, 3180, 1702, 1678	2.71 (3H, d, *J* = 0.8, 10-CH_3); 2.81 (1H, dd, *J* = 4.5, *J* = 13.7, CH_2); 2.95 (1H, dd, *J* = 10.5, *J* = 13.4, CH_2); 4.07 (3H, s, OCH_3); 4.42 (1H, s, NH); 5.11 (1H, dd, *J* = 4.0, *J* = 10.3, CH); 7.31-7.43 (5H, m, H Ar); 7.59 (1H, s, H-11); 7.72 (1H, s, H-6); 7.92 (1H, q, *J* = 0.8, H-9); 8.84 (1H, br. s, NH)
6b	3319, 3217, 1718, 1674	1.25 (3H, d, *J* = 6.1, 4-CH_3); 2.39 (1H, dd, *J* = 9.4, *J* = 13.2, CH_2); 2.65 (1H, ddd, *J* = 1.1, *J* = 5.2, *J* = 13.2, CH_2); 2.72 (3H, d, *J* = 0.8, 10-CH_3); 3.00 (3H, s, 5-CH_3); 3.93 (1H, m, CH); 4.08 (3H, s, OCH_3); 7.54 (1H, s, H-11); 7.83 (1H, s, H-6); 7.96 (1H, q, *J* = 0.8, H-9); 8.48 (1H, br. s, NH)
6c	3350, 1734, 1660	1.32 (3H, d, *J* = 6.2, 4-CH_3); 2.35 (1H, dd, *J* = 8.0, *J* = 13.1, CH_2); 2.63 (1H, dd, *J* = 5.2, *J* = 13.1, CH_2); 2.73 (3H, d, *J* = 0.8, 10-CH_3); 3.52 (3H, s, 5-CH_3); 3.75 (1H, br. s, NH); 4.10 (1H, m, CH); 4.06 (3H, s, OCH_3); 7.69 (1H, s, H-6); 7.70 (1H, s, H-11); 7.96 (1H, q, *J* = 0.8, H-9)
8	3312, 3260, 3193, 1738, 1698	3.58 (3H, s, OCH_3); 3.75 (2H, br. s, CH_2); 4.00 (3H, s, OCH_3); 7.56-7.68 (3H, m, H Ar); 7.77 (1H, d, *J* = 9.2, H-6); 8.11-8.17 (2H, m, H Ar); 8.14 (1H, d, *J* = 9.1, H-7); 8.17 (1H, s, H-10); 11.22 (1H, br. s, NH)
9	3600-3000, 1732, 1673	2.52 (1H, dd, *J* = 4.7, *J* = 13.6, C(10)H_2); 2.64 (1H, dd, *J* = 6.2, *J* = 13.7, C(10)H_2); 3.54 (3H, s, OCH_3); 3.70 (2H, br. s, C(3)H_2); 3.76 (3H, s, OCH_3); 4.21 (1H, dd, *J* = 4.8, *J* = 5.8, CH); 4.82 (1H, br. s, NH); 5.47 (1H, br. s, OH); 6.58 (1H, d, *J* = 8.8, H-7); 6.83 (1H, d, *J* = 8.8, H-6); 7.40-7.55 (3H, m, H Ar); 8.00-8.10 (2H, m, H Ar); 9.01 (1H, br. s, NHCO)
10	3315, 3199, 1739, 1715, 1673	2.20 (3H, s, CH_3); 3.00-3.14 (2H, m, CH_2); 3.55 (2H, br. s, C(3')H_2); 3.75 (3H, s, OCH_3); 4.45 (1H, m, H-2); 4.59 (1H, br. s, 2-NH); 6.59 (1H, dd, *J* = 2.7, *J* = 8.7, H-8'); 6.70 (1H, d, *J* = 2.7, H-6'); 6.93 (1H, d, *J* = 8.7, H-9'); 7.43-7.52 (3H, m, H Ar); 8.06-8.13 (2H, m, H Ar); 8.80 (1H, br. s, H-1')
1a	3467, 3376, 3335, 3185, 1660	2.65 (1H, ddd, *J* = 1.2, *J* = 4.0, *J* = 13.2, CH_2); 2.86 (1H, dd, *J* = 10.2, *J* = 13.2, CH_2); 3.48 (1H, br. s, NH); 3.67 (2H, br. s, NH_2); 4.98 (1H, dd, *J* = 4.0, *J* = 10.4, CH); 6.16 (1H, d, *J* = 2.4, H-6); 6.28 (1H, dd, *J* = 2.4, *J* = 8.3, H-8); 6.75 (1H, d, *J* = 8.3, H-9); 7.26-7.37 (5H, m, H Ar); 7.76 (1H, br. s, NHCO)
7		3.58 (2H, br. s, CH_2); 3.75 (2H, br. s, NH_2); 6.62 (1H, dd, *J* = 2.6, *J* = 8.5, H-8); 6.80 (1H, d, *J* = 2.6, H-6); 6.89 (1H, d, *J* = 8.5, H-9); 7.45-7.52 (3H, m, H Ar); 7.70 (1H, br. s, NHCO); 8.08-8.13 (2H, m, H Ar)

The structures of compounds **2** and **3** were confirmed by ^{1}H and ^{13}C NMR spectra (Tables 2 and 3). In the ^{1}H NMR spectrum of compound **3** three singlet signals were observed for the aromatic protons of the benzene and pyridine rings, two singlets for the methoxycarbonyl groups at 4.05 and 4.09 ppm. The chemical shifts of the protons of the diazepine hetero ring were changed insignificantly compared to the initial amine **1a**. This shows the linear structure of the condensed system. In the spectrum of compound **2** the two doublets observed at 7.59 and 7.97 and the singlet at 8.52 ppm in the aromatic region show the angular addition of the pyridine ring. In addition, in the spectrum only one signal of metoxycarbonyl groups was obserwed, the signal for the amino group proton at N(5) was absent, and the signal of the methine proton of the diazepine nucleus was displaced by 1 ppm towards lower field in comparison with compound **3**, which indicates the formation of the fourth ring. The ^{13}C NMR spectra confirm the structures of compounds **2** and **3**.

The formation of compounds **2** and **3** indicates that the cyclocondensation occurs at positions 6 and 8 of amine **1a** similar. It should be mentioned that in the analogous interaction of 5-unsubstituted 7-amino-4-methyl-benzodiazepines with glutaconate only one product is formed, the tetracyclic indole derivative [1, 2]. The different direction of the reaction is seemingly caused by the influence of the 4-phenyl group of the initial amine **1a** on the activity of positions 6 and 8 of the benzene ring. The activity in these positions of compound **1a** is demonstrated by calculations of the ionization energy I_{min} (Table 4). The close values of I_{min} (C(6) 366.42 and C(8) 366.41 kcal/mol) indicates that the process of extracting an electron (ionization) occurs with the same probability at atoms C(6) and C(8). For comparison values are given for I_{min} of amine **1c**, which are cyclized with glutaconate in position 6 of the benzene ring.

TABLE 3. ^{13}C NMR Spectrum of Compounds **1a**, **2-5**, **6a-c**, **8**, and **10**

Com-pound	Chemical shifts, δ, ppm
2	43.14 (C-7); 51.77 (C-6); 52.86 (OCH_3); 118.17, 121.00, 121.30, 123.75, 124.16, 125.52 (2C); 127.56, 127.99, 128.68 (2C); 133.13, 138.77, 141.47, 148.49, 163.08 (CO); 164.92 (CO); 170.35 (8-CO)
3	41.66 (C-3); 52.86 (OCH_3); 53.28 (OCH_3); 61.77 (C-4); 116.69 (C-11); 118.15 (C-6); 120.75 (C-9); 122.21, 125.81 (2C); 128.43, 129.17 (2C); 133.30, 134.10, 141.90, 143.69, 146.95, 147.69, 165.35 (CO); 166.02 (CO); 171.29 (2-CO)
4	43.15 (C-7); 51.75 (C-6); 118.10, 120.76, 121.08, 123.75, 124.09, 125.54 (2C); 127.55, 127.74, 128.69 (2C); 133.02, 138.82, 141.55, 150.80, 163.78 (CO); 166.05 (CO); 170.31 (8-CO)
5	42.02 (C-3); 59.91 (C-4); 115.74, 115.85, 118.77, 120.42, 126.33 (2C); 127.46, 128.48 (2C); 133.68, 135.24, 143.66, 144.29, 146.90, 146.93, 166.15 (CO); 167.37 (CO); 170.48 (2-CO)
6a	18.82 (10-CH_3); 41.37 (C-3); 53.13 (OCH_3); 62.49 (C-4); 115.26 (C-11); 119.08 (C-6); 120.31 (C-9); 125.25, 125.81 (2C); 128.35, 129.12 (2C); 131.76, 141.48, 143.99, 144.92, 146.31, 147.20, 166.15 (8-CO); 171.82 (2-CO)
6b	16.75 (10-CH_3); 18.78 (4-CH_3); 39.36 (5-CH_3); 40.04 (C-3); 53.17 (OCH_3); 60.91 (C-4); 114.56 (C-11); 120.73 (C-9); 121.18 (C-6); 125.38, 134.96, 144.51, 144.78, 146.40, 146.98, 166.17 (8-CO); 172.81 (2-CO)
6c	18.85 (10-CH_3); 22.75 (4-CH_3); 36.48 (1-CH_3); 40.09 (C-3); 53.09 (OCH_3); 55.66 (C-4); 115.88 (C-6); 120.60 (C-9); 120.69 (C-11); 125.83, 139.94, 142.06, 144.98, 145.98, 147.30, 166.07 (8-CO); 170.77 (2-CO)
8	C-3 is overlapped by the solvent signal; 52.46 (OCH_3); 52.75 (OCH_3); 120.03, 122.28, 126.80, 128.31 (2C); 128.46, 128.84 (2C); 129.04, 131.45, 131.73, 135.82, 139.83, 145.30, 146.32, 155.92, 164.47 (CO); 165.17 (CO); 168.06 (CO)
9	36.04, 40.16, 50.86, 52.32, 52.68, 71.58, 115.33, 116.45, 121.17, 123.06, 127.80 (2C); 128.73 (2C); 131.29, 136.88, 137.82, 140.94, 158.76, 166.50, 173.13, 176.19
10	36.04 (CH_3); 39.88 (C-3'); 45.41 (C-3); 52.60 (CH_3O); 52.66 (C-2); 110.14 (C-6'); 113.91 (C-8'); 121.25, 122.92 (C-9'); 127.66 (C-2",6"); 128.61 (C-3",5"); 130.85 (C-4"); 137.74 (C-1"); 140.99, 143.79, 158.82, 167.16 (CO); 173.00 (CO); 205.85 (CO)
1a	41.41 (CH_2); 63.37 (CH); 106.98, 108.62, 119.49, 123.69, 125.94 (2C); 128.01, 128.92 (2C); 139.43, 144.66, 144.90, 171.84

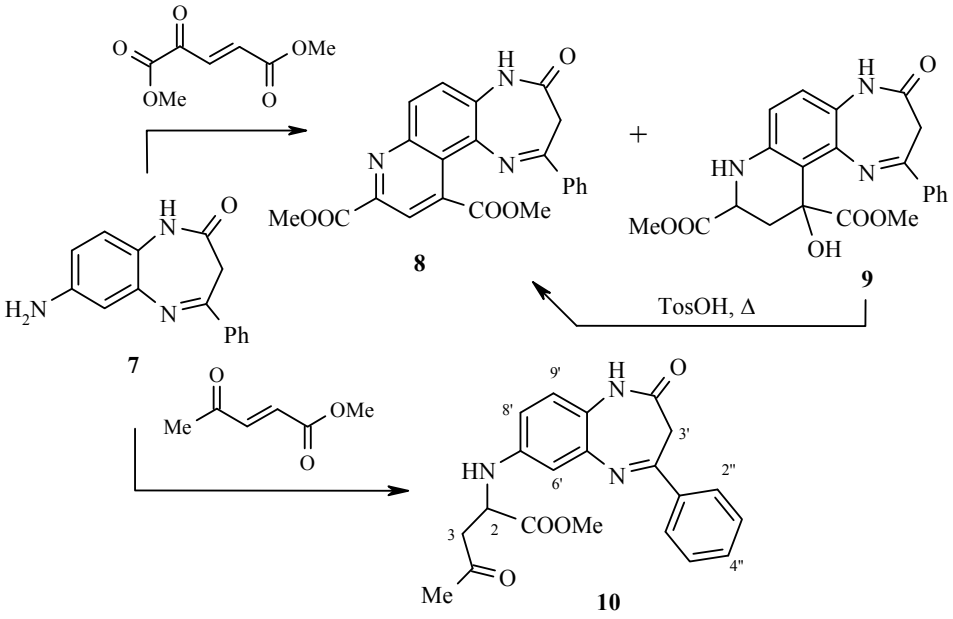
TABLE 4. Values of I_{min} on the Carbon Atoms of the Benzene Ring and on the Nitrogen Atom of the Primary Amino Group of Compounds **1a,c** and **7**

Compound	I_{min}, kcal/mol				
	C(6)	C(7)	C(8)	C(9)	N(7)
1a	366.42	401.71	366.41	398.10	366.88
1c	358.28	399.40	380.49	381.64	358.58
7	365.27	401.71	369.42	377.49	382.10

Compounds containing the 2,4-dicarboxypyridine fragment are substances imitating the structure of glutamic acid. Similar compounds were studied as inhibitors of L-glutamate transport in [6]. We carried out alkaline hydrolysis of methyl esters **2** and **3**. After stirring for 3 h at room temperature in aqueous methanolic solution in the presence of 1 N NaOH the corresponding acids **4** and **5** were isolated. The obtained compounds were brightly colored crystalline substances.

By reacting 7-amino-4-phenyl(or methyl)benzodiazepinones **1a-c** with methyl 4-oxo-2-pentenoate only 10-methyl-substituted [1,4]diazepino[2,3-*g*]quinolines **6a-c** were synthesized, i.e. cyclization occurs at position 8 of the benzene ring of the initial amines. In the interaction of amine **1c** with glutaconate, cyclization occurred at position 6 of the benzene ring [2]. The change of direction of the reaction is probably linked with the spatial effect of the methyl group. The Taft's constants of the methyl and carboxyl groups [7] indicate that the methyl group has a more expressed steric action on the course of the reaction than the carboxyl group. Consequently in the interaction of amines **1a** and **1c** with methyl 4-oxo-2-pentenoate the methyl group next to the cyclizaton reaction center shows a more expressed steric hindrance to the course of the reaction at position 6 of the benzene ring in comparison with the effect of the carboxyl grouping in the interaction of amines **1a** and **1c** with glutaconate. It is evident that in the present case the decisive effect on the course of cyclization proved to be the resonance stabilization energy and not the ability of the initial amines to ionize (delivery of an electron). The stabilization energy of amine **1c** at C(8) is greater by 5 kcal/mol than the stabilization energy at C(6) (238.63 and 233.21 kcal/mol respectively), consequently cyclization occurs preferentially at position 8 of amine **1c** with the formation of the energetically more favored structure **6c**. The difference in the stabilization energy of amine **1a** at atoms C(6) and C(8) is less (C(6) 235.33 and C(8) 237.21 kcal/mol), but the tendency of the energy advantage towards cyclization at position 8 with the formation of **6a** is retained.

Scheme 2



The ^{1}H NMR spectra indicate a linear coupling of rings in compounds **6a-c**, in which two separate signals are displayed for the protons of the benzene ring and a quartet is displayed for the proton at atom C(9) of the pyridine ring (J = 0.8 Hz). The position of the methyl group in the pyridine ring of compounds **6a-c** is unequivocally established by the NOE method, and further confirms that the first step of the cyclocondensation reaction is the nucleophilic addition of the primary amino group to the β-carbon of the unsaturated ketone.

The condensation of 7-amino-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one (**7**) with α,β-unsaturated ketones (Scheme 2) proceeds in an unusual way. Two compounds were obtained by the interaction of 1,5-benzodiazepin-2-one **7** with glutaconate, *viz.* [1,4]diazepino[2,3-*f*]quinoline **8** and piperidinol derivative **9** (yields of 19 and 31% respectively).

The cycloaddition therefore occurs at position 6 of the benzene ring of amine **7**, which agrees with the value of I_{min} at the C(6) and C(8) atoms of compound **7**. Under the reaction conditions dehydration of product **9** does not occur completely. The formation of the piperidinol derivative is described in [5]. The presence in the ^{1}H NMR spectrum of compound **9** of two doublet signals at 6.58 and 6.83 ppm confirmed the angular cycloaddition. Signals were also observed for the protons of the ABX system of the CH_2CH fragment, for the amino group proton N(8)–H at 4.82 ppm, two methyl singlets (3.54 and 3.76 ppm), and a broadened singlet for the OH proton at 5.47 ppm, indicating the formation of the piperidine ring. In addition derivative **8** was synthesized by boiling compound **9** in dichloromethane solution in the presence of *p*-toluenesulfonic acid. In the reaction of amine 7 with pentenoate no cyclic derivative was formed but the product **10** was practically exclusively that of addition of unsaturated ketone to the primary amino group. On chromatography of the reaction mixture no cyclization products were detected. In favor of the formation of methyl pentenoate **10** are the position of the signals in the ^{1}H NMR spectrum and the multiplicity of the diazepine and benzene protons were changed insignificantly in comparison with the initial amine **7***. Also observed were the signals of the ABX protons of the CH_2CH fragment, two singlet signals at 2.20 and 3.75 ppm belonging to the COMe and COOMe groups respectively, and in place of the signal of the NH_2 protons a broadened signal appeared for the NH group at 4.59 ppm. The data of the IR and ^{13}C NMR spectra were not at variance with the proposed formula.

The initial amine **1a** was synthesized by the hydrogenation of 7-nitro-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one over 10% Pd/C. Syntheses of the dihydronitro derivative and amine **7** are described in [8]. Amines **1b,c** were obtained according to [2].

EXPERIMENTAL

The IR spectra (KBr disks) were recorded on a Perkin-Elmer Spectrum GXFT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity Inova 300 spectrometer (300 and 75 MHz respectively) in $CDCl_3$ (compounds **1a**, **3a**, **6a-c**, **7**, **9**, **10**) and in DMSO-d_6 (compounds **2**, **4**, **5**, **8**). Assignment of signals in the ^{1}H NMR spectra was based on their integral intensities, multiplicity, and size of chemical shifts using NOE and COSY methods, and also APT and HETCOR for ^{13}C NMR spectra. Chemical shifts were referred to TMS (δ^1(H) = 0 ppm) and to the solvent signal for $CDCl_3$ ($\delta(^{13}C)$ = 77.0 ppm) and DMSO-d_6 ($\delta(^{13}C)$ = 39.5 ppm). The melting points of the synthesized compounds were determined in capillaries on a MEL-TEMP 1202D instrument and are not corrected. A check on the progress of reactions and the purity of the obtained compounds was effected by TLC on Silicagel 60F TLC plates (Merck), eluent was chloroform–ethyl acetate–methanol, 14:7:1, developing with a UV detector. Silica gel L5/40 μm (Chemapol) was used for column chromatography in the system dichloroethane–ethyl acetate with a gradient from 10:0 to 10:5 [9].

*The ^{1}H NMR spectrum of compound **7** is given in Table 2 since no spectral data were given in [8].

Quantum-chemical calculations were carried out using the B3LYP functional and 6-31G* basis with complete optimization of the geometric structures with SPARTAN 06 programs [11]. Values of the local ionization energy I_{min} obtained on the molecular electron density surface, were equal to 0.025 electron/Bohr radius^3.

Dimethyl 2-oxoglutaconate was synthesized from 2-oxoglutaric acid according to [6], methyl 4-oxo-2-pentenoate was synthesized analogously from 3-bromolevulinic acid methyl ester [10].

Methyl Ester of 4,8-Dioxo-6-phenyl-6,7,8,9-tetrahydro-4H-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-*cd*]-indole-2-carboxylic Acid (2) and Dimethyl Ester of 2-Oxo-4-phenyl-2,3,4,5-tetrahydro-1H-[1,4]-diazepino[2,3-*g*]quinoline-8,10-dicarboxylic Acid (3). A solution of aminobenzodiazepinone **1a** (1.27 g, 5.0 mmol) and dimethyl 2-oxoglutaconate (1.28 g, 7.5 mmol) in absolute dichloromethane (300 ml) was stirred at room temperature for 24 h. A 3 N solution of hydrochloric acid in glacial acetic acid (4 ml, 12.0 mmol) was added and the mixture stirred a further 24 h at room temperature. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture to pH 7 in the aqueous layer. After separating, the organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was chromatographed, collecting fractions with R_f 0.50 (**2**) and 0.68 (**3**), evaporated, and recrystallized. Compound **2** (0.4 g), sandy-colored crystals, and compound **3** (0.5 g), orange crystals were obtained.

Methyl Esters of 1-R^1-4-R^2-5-R^3-10-methyl-2-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[2,3-*g*]-quinoline-8-carboxylic Acids 6a-c were obtained analogously from the appropriate aminobenzodiazepinones **1a-c** (5 mmol) and methyl 4-oxo-2-pentenoate (0.96 g, 7.5 mmol). After evaporating the organic phase the solid residue was recrystallized. Compound **6a** (0.95 g), compound **6b** (0.62 g), and compound **6c** (0.60 g) were obtained as yellow crystals.

Dimethyl Ester of 4-Oxo-2-phenyl-4,5-dihydro-3H-[1,4]diazepino[2,3-*f*]quinoline-9,11-dicarboxylic Acid (8) and Dimethyl Ester of 11-Hydroxy-4-oxo-2-phenyl-4,5,8,9,10,11-hexahydro-3H-[1,4]diazepino-[2,3-*f*]quinoline-9,11-dicarboxylic Acid (9) were obtained analogously from dihydrobenzodiaze-pinone **7** (1.26 g, 5.0 mmol) and dimethyl 2-oxoglutaconate (1.28 g, 7.5 mmol) in a mixture (400 ml) of absolute dichloromethane–THF, 1:1. The solvent was evaporated, the residue suspended in chloroform, and compounds **8** and **9** isolated as described for compounds **2** and **3**. Compound **8** (R_f 0.52) (0.4 g) was obtained as yellow crystals. Hexane was added to the residue of fractions with R_f 0.38, the solid filtered off, and compound **9** (0.65 g, 31%) was isolated as sandy-colored crystals, mp 108°C (decomp.). The substance was unstable and was not purified by crystallization.

Methyl Ester of 4-Oxo-2-[(2-oxo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-7-yl)amino]pentanoic Acid (10) was obtained from dihydrobenzodiazepinone **7** (1.26 g, 5.0 mmol) and methyl 4-oxo-2-pentenoate (0.96 g, 7.5 mmol) analogously to that described for compounds **8** and **9**. Compound **10** (1.4 g) (R_f 0.37) was obtained.

Preparation of Compound 8 by Dehydration of Compound 9. A solution of compound **9** (0.5 g, 1.2 mmol) and *p*-toluenesulfonic acid (0.21 g, 1.2 mmol) in abs. CH_2Cl_2 (100 ml) was boiled for 3 h. The reaction mixture was cooled, and saturated aqueous $NaHCO_3$ solution was added to pH **7** in the aqueous layer. After separation the organic phase was washed with water, dried over $MgSO_4$, and evaporated to dryness. The obtained residue was wetted with *t*-BuOMe and filtered off. Compound **8** (0.2 g, 42%) was obtained, having mp 309-311°C. A test sample mixed with samples obtained by various methods gave no depression of melting point.

4,8-Dioxo-6-phenyl-6,7,8,9-tetrahydro-4H-[1,4]diazepino[3,2,1-*hi*]pyrido[4,3,2-cd]indole-2-carboxylic Acid (4). A 1 N solution of NaOH (10 ml) was added with stirring to a suspension of compound **2** (0.19 g, 0.5 mmol) in aqueous MeOH (1:1) (40 ml). The bright raspberry-colored solution obtained was stirred for 1 h at room temperature, and solvent (about 20 ml) was evaporated in vacuum. The aqueous solution was extracted with chloroform, and acidified with 1 N HCl solution. After cooling, the precipitated light–orange solid was filtered off, and acid **4** (0.11 g) was obtained.

2-Oxo-4-phenyl-2,3,4,5-tetrahydro-4H-[1,4]diazepino[2,3-*g*]quinoline-8,10-dicarboxylic Acid (5). Compound **5** was obtained analogously as dark-cherry crystals from compound **3** (0.2 g, 0.5 mmol).

7-Amino-4-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (1a). A suspension of 7-nitro-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-one [8] (5.62 g, 20.0 mmol) in MeOH (500 ml) was hydrogenated in the presence of 10% Pd/C catalyst. After absorption of hydrogen (1.79 l, 80 mmol), the catalyst was filtered off, the solvent evaporated, and the solid residue recrystallized from EtOAc–ether. Compound **7** (3.9 g, 77%) was obtained as light-gray crystals; mp 159-161°C. Found, %: C 71.30; H 5.89; N 16.71. $C_{15}H_{15}N_3O$. Calculated, %: C 71.13; H 5.97; N 16.59.

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